

*epi*TRENDS

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Cryptococcus gattii in the Pacific Northwest

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A recently published article⁽¹⁾ generated national media coverage about *Cryptococcus gattii*, a previously little-known fungus. There are many cryptococcal species. *Cryptococcus neoformans* (variants *neoformans* and *grubii*) is an opportunistic pathogen affecting primarily HIV-infected and other immunocompromised persons; it is associated with pigeon guano and contaminated soil. *Cryptococcus gattii*, associated with trees and soil, also causes human illness but more rarely and it affects both immunocompetent and immunocompromised persons. Other cryptococcal species, such as *C. laurentii* and *C. albidus*, very rarely cause illness in persons with underlying conditions that impair their immune response.



Washington State forest

C. gattii is associated with trees
and soil in the
Pacific Northwest

Photo courtesy of Tom Green

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Discussion Points

Here are three discussion points related to the public health response for *C. gattii*. The answers are contained in the text, or you may refer to the answers at the end of this article.

1. Why is it important to distinguish infections caused by *C. neoformans* and *C. gattii*?
2. What should be done during public health investigations of *C. gattii* infections?
3. What is the case fatality ratio for *C. gattii*? Why is it so elevated?



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Emergence of *C. gattii*

Cryptococcus gattii was previously known only in tropical and subtropical climates until emerging in the Pacific Northwest in 1999 on Vancouver Island, British Columbia (BC). The organism has been repeatedly isolated from certain types of trees and geoclimatic zones on Vancouver Island, indicating that it has adapted to a temperate climate. By 2007, 218 human cases (19 deaths; case fatality ratio [CFR]: 9%) were identified in the ensuing BC outbreak, along with numerous animal cases and environmental positives. Initially, all cases either lived on or had traveled to Vancouver Island, but cases were subsequently identified on the BC mainland and in the United States, indicating the presence of *C. gattii* in other areas of the Pacific Northwest.

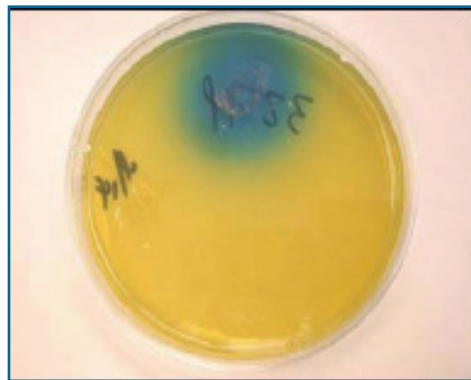
Since 2004, when cases were first recognized in the United States, 57 human cases (10 deaths; CFR: 18%) and 50 animal cases have been identified in Washington, Oregon, California, and Idaho. Since 2006, 15 human cases (3 deaths) have been reported in Washington; 23 animal cases have been reported since 2004. Apparently high case-fatality rates, particularly among US cases, likely reflect under-diagnosing and underreporting of *C. gattii* infections, especially less severe cases. This highlights the need for improved surveillance.

Transmission and Pathogenesis

Infection occurs when inhaled cryptococcal spores colonize the nasal cavity or sinuses and then spread to other body sites. The conditions needed for spore dispersal, inhalation, infection and propagation are not well defined. The incubation period is estimated as 2 to 13 months. Meningitis and pneumonia are the predominant presentations. Symptoms can include prolonged cough, shortness of breath, chest pain, fever, headache, weight loss, and night sweats. Compared to *C. neoformans*, *C. gattii* tends to cause more lung, brain, or muscle cryptococcomas (large masses) and may respond more slowly to antifungal therapy than *C. neoformans*. Both animals and humans can be infected, but the disease is not transmitted between or within species.

Laboratory Diagnosis

Cryptococcal antigen tests are available commercially but cannot distinguish *C. gattii* from *C. neoformans*. A fungal culture from CSF, blood, sputum, or tissue biopsy is required for speciation. The species can be identified by using canavanine-glycine-bromothymol blue (CGB) agar or genomic sequencing.



C. gattii produces a blue color change when plated on CGB agar.

Photo courtesy of Karen Bartlett
University of British Columbia, Canada

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Cryptococcus gattii has four genotypes: VGI, VGII (subtypes a, b, and c), VGIII, and VGIV. Genotype and subtype both correlate with geographic distribution and are important parts of the epidemiologic investigation. Serotypes may be useful too: serotypes A, D, and AD are *C. neoformans*, whereas serotypes B or C are *C. gattii*.

Surveillance and Investigation

Questions remain about characteristics of genotypes, the organism's ecologic niche, risk factors for infection, and treatment. Washington State Department of Health (DOH) is working with BC Centre for Disease Control, US Centers for Disease Control and Prevention (CDC), and other state and local health departments to conduct surveillance for *C. gattii* and better define the epidemiology of this emerging disease. Data from BC suggest that animal cases precede human cases and thus may be valuable sentinel indicators. Veterinary reporting of animal cases may also provide important clues about *C. gattii* distribution because travel for pets tends to be limited. Molecular subtype data seem to correlate with exposure location: the majority of BC and northern Washington isolates are VGIIa, whereas southern Washington and Oregon have isolated a higher proportion of VGIIc. However, we have not seen an association between molecular subtype and death. We hope to increase awareness among physicians and veterinarians, and we encourage physicians to maintain an index of suspicion for *C. gattii* when treating any cryptococcal infection, but particularly when treating HIV-negative or immunocompetent patients with symptoms consistent with cryptococcal disease.

To distinguish the species, clinical cryptococcal isolates should be submitted to a laboratory that has CGB medium, which is not widely available. If necessary, testing can be done at CDC but arrangements must be made through DOH Communicable Disease Epidemiology Section. Clinicians should send isolates identified as *C. gattii* to Washington State Public Health Laboratories for confirmation and genotyping at CDC.

Cases of *C. gattii* should be reported as rare diseases of public health significance (<http://www.doh.wa.gov/notify/nc/cryptococcus.htm>). Given the long incubation period, investigators should obtain detailed exposure histories for a period of 13 months prior to illness

The form is titled "Cryptococcal Disease" and is designed for reporting cases to the Washington State Department of Health (DOH). It includes sections for:

- Reporting Information:** LHI Use, ID, Date, LHI Classification, Confirmed/Probable, County, Outbreak # (LHI), and DOH Use/ID/Date Received.
- REPORT SOURCE:** Initial report date, Reporter (check all that apply: Lab, Hospital, HCP, Public health agency, Other), Investigation start date, Reporter name, Reporter phone, Primary HCP name, and Primary HCP phone.
- PATIENT INFORMATION:** Name (last, first), Address, City/State/Zip, Phone(s)/Email, Alt. contact (Parent/guardian, Spouse, Other), Name, Phone, Occupation/grade, Employer/worksite, School/child care name, Birth date, Age, Gender, Ethnicity, Race (check all that apply: Amer Ind/Alk Native, Asian, Native HI/other PI, Black/Afr Amer, White, Other, Unk).
- CLINICAL INFORMATION:** Onset date, Diagnosis date, Illness duration, Asymptomatic status, Signs and Symptoms (Fever, Highest measured temp, Oral, Rectal, Other, Chills, Night sweats, Loss of appetite, Weight loss, Nausea, Cough, Shortness of breath, Chest pain, Headache, Neck stiffness, Muscle pain), Preexisting Conditions (Preexisting medical condition which may have contributed to current illness or death, Previously healthy, HIV positive, Immunosuppressive therapy or disease, Organ transplant, Chronic diabetes, Chronic lung disease, Cancer, solid tumors, or hematologic malignancies, Current tobacco smoker, Former tobacco smoker, Taking oral steroids (e.g. cortisone, prednisone) in the year before onset).
- Clinical Findings:** Y/N/DK/NA for Encephalitis or encephalomyelitis, Meningitis, Brain cryptococcoma, Pneumonia, X-ray confirmed, Lung cryptococcoma, Skin abscess, and Other.
- Hospitalization:** Y/N/DK/NA for Hospitalized at least overnight for this illness, Hospital name, Admit date, Discharge date, Y/N/DK/NA for Died from illness, Death date, Y/N/DK/NA for Autopsy, Place of death.
- Laboratory:** Collection date, Source, Y/N/DK/NA for Cryptococcus identified from fungal culture, How was it identified? (Cryptococcus identified from cytology, Cryptococcus identified from histopathology, Positive serology), Y/N/DK/NA for Species identified, Result, Y/N/DK/NA for Variant identified (e.g. VGIIa), Result.

 At the bottom, it states "Answers are: Yes, No, Unknown to case, Not asked /Not answered" and "DOH 420-011 (Rev. 2/17/10)".

Use this form to report a case of *Cryptococcus gattii* as a rare disease of public health significance in Washington State

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onset (see <http://www.doh.wa.gov/notify/forms/cryptococcus.pdf>). Travel history should be carefully evaluated, including within Washington, BC, other areas of the Northwest, or other countries considered to be endemic. Risk exposures are still poorly defined, but may include soil disturbance (large scale activities such as excavation or landscaping are probably higher risk than gardening, mulching or digging), residence next to a construction site or wooded area, and occupations such as construction or logging. Smoking may also be a risk factor. DOH offers limited environmental testing during case investigations.

Answers to Public Health Discussion Questions:

1. Although *C. gattii* is well-known in Africa and Australia, *C. gattii* infections were first noted in the Northwest in 1999. Infection with *C. gattii* only recently became a notifiable condition in BC (2003) and reporting requirements are still being determined in the United States. Because there is likely a high degree of underreporting of this emerging infectious disease, several Northwest public health agencies are trying to characterize the geographic distribution, prevalence, and molecular type of *C. gattii* infections. To do this, it is important to differentiate infections due to *C. gattii* from those due to *C. neoformans*. Speciation requires an isolate from a fungal culture, so diagnosis must include more than just a cryptococcal antigen (CrAg) test. Clinically, differentiating the species may be helpful because *C. gattii* may respond more slowly to antifungal treatment.
2. Initially, all cryptococcal isolates should be speciated to distinguish between *C. neoformans* and *C. gattii* infections. DOH can arrange testing to identify species and can forward *C. gattii* isolates to CDC for genotyping. If *C. gattii* is identified, the primary goal of the investigation should be to identify potential sites of exposure. Because the incubation period may be up to 13 months, this can be difficult. Examples of situations for exposure include proximity to excavation sites, participation in landscaping projects, and occupational exposure as loggers or construction workers.
3. Of identified cases of *C. gattii*, more than 5% of ill people die. The case fatality ratio (CFR) is the number of KNOWN deaths over the number of KNOWN cases. Frequently, when working with emerging infections, the most severe or often fatal cases are more likely to be identified. Less severe, nonfatal, or resolved cases often go unreported. Consequently, emerging infectious diseases may often have an elevated CFR that decreases as more cases are identified. This is another public health reason why identifying all *C. gattii* human infections is important to understanding the full spectrum of disease.

Reference

- (1) Byrnes EJ III, Li W, Lewit Y, et al. Emergence and Pathogenicity of Highly Virulent *Cryptococcus gattii* Genotypes in the Northwest United States. PLoS Pathog 2010;6(4): e1000850.